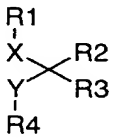
CLAIMS

1. A pharmaceutical formulation, comprising:
(i) an inhibitor of carboxypeptidase U or a pharmaceutically acceptable salt thereof, and
(ii) a thrombin inhibitor or a derivative thereof, in
admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

2. The pharmaceutical formulation according to claim 1, wherein the inhibitor of carboxypeptidase U is a compound of general formula I



(I)

or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, wherein

R_1 represents,

C_1-C_6 alkyl, substituted with one or more basic groups such as amino, amidino and/or guanidino;

cycloalkyl, substituted with one or more basic groups such as amino, amidino and/or guanidino;

heterocyclyl, containing at least one nitrogen atom;

heterocyclyl, containing at least one hetero atom selected from S or O, and substituted with one or more basic groups such as amino, amidino and/or guanidino;

or aryl, substituted with one or more basic groups such as amino, amidino and/or guanidino,

R_2 represents H, acyl, acylamino, alkyl, alkylcarbamoyl, alkylthio, alkoxy, aroyl, aroylamino, aryloxy, arylthio, amidino, amino, aryl, carbamoyl, carboxy, cyano, cycloalkyl, formyl, guanidino, halogen, heterocyclyl, hydroxy, oxo, nitro, thiol, Z_2N-CO-O-, ZO-CO-NZ- or Z_2N-CO-NZ- group,

R_3 represents $COOR_5$, $SO(OR_5)$, SO_3R_5, $P{=}O(OR_5)_2$, $B(OR_5)_2$, $P{=}OR_5(OR_5)$, or tetrazole, or any carboxylic acid isostere,

R_4 represents SH, S-CO-C_1-C_6 alkyl or S-CO-aryl,

R_5 represents H, C_1-C_6 alkyl or aryl,

R_6 represents H or C_1-C_6 alkyl,

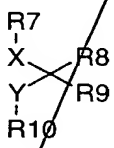
X represents O, S, SO, SO_2, $C(Z)_2$, N(Z), NR_6SO_2, SO_2NR_6, NR_6CO or $CONR_6$,

Y represents $C(Z)_2$,

Z represents independently H, C_1-C_6 alkyl, aryl, cycloalkyl or heterocyclyl.

3. The pharmaceutical formulation according to claim 1, wherein the inhibitor of carboxypeptidase U is a compound of general formula II,

(ii) a compound of general formula II



(II)

or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt, wherein

R_7 represents,

C_1-C_6 alkyl, substituted with one or more basic groups such as amino, amidino and/or guanidino;

cycloalkyl, substituted with one or more basic groups such as amino, amidino and/or guanidino;

heterocyclyl, containing at least one nitrogen atom;

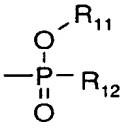
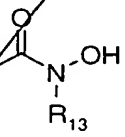
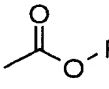
heterocyclyl, containing at least one hetero atom selected from S or O, and substituted with one or more basic groups such as amino, amidino and/or guanidino;

or aryl, substituted with one or more basic groups such as amino, amidino and/or guanidino,

R_8 represents H, acyl, acylamino, alkyl, alkylcarbamoyl, alkylthio, alkoxy, aroyl,

aroylamino, aryloxy, arylthio, amidino, amino, aryl, carbamoyl, carboxy, cyano, cycloalkyl, formyl, guanidino, halogen, heterocyclyl, hydroxy, oxo, nitro, thiol, Z_2N-CO-O-, ZO-CO-NZ- or Z_2N-CO-NZ- group,

R_9 represents $COOR_{11}$, $SO(OR_{11})$, SO_3R_{11}, $P{=}O(OR_{11})_2$, $B(OR_{11})_2$, $P{=}OR_{11}(OR_{11})$, or tetrazole, or any carboxylic acid isostere,

R_{10} represents a  -group, or a  -group, or a  -group, roup,

R_{11} represents H, C_1-C_6 alkyl or aryl,

R_{12} represents C_1-C_6 alkyl, aryl, cycloalkyl, heterocyclyl, or an optionally N-substituted H_2N-C(Z)-CONH-C(Z)- or H_2N-C(Z)- group,

R_{13} represents H or C_1-C_6 alkyl,

X represents O, S, SO, SO_2, $C(Z)_2$, N(Z), $NR_{13}SO_2$, SO_2NR_{13}, $NR_{13}CO$ or $CONR_{13}$,

Y represents O, N(Z), S, $C(Z)_2$, or a single bond,

Z represents independently H, C_1-C_6 alkyl, aryl, cycloalkyl or heterocyclyl,

with the proviso that when X represents O, S, SO, SO_2, N(Z), NR_7SO_2, SO_2NR_7, or NR_7CO then Y represents $C(Z)_2$ or a single bond.

4. The pharmaceutical formulation according to any previous claim, wherein the thrombin inhibitor is a low molecular weight thrombin inhibitor.

5. The pharmaceutical formulation according to claim 4, wherein the low molecular weight thrombin inhibitor is a peptide-based, amino acid-based, and/or peptide analogue-based, thrombin inhibitor with one to four peptide linkages.

6. The pharmaceutical formulation according to claim 5, wherein the low molecular weight thrombin inhibitor is HOOC-CH_2-(R)Cgl-Aze-Pab-H or a prodrug thereof.

7. The pharmaceutical formulation according to claim 6, wherein the prodrug is EtOOC-CH_2-(R)Cgl-Aze-Pab-OH.

8. The pharmaceutical formulation according to any previous claim, wherein the molar ratio between the inhibitor of carboxypeptidase U and the thrombin inhibitor lies in the range of from about 1000:1 to about 1:1000, preferably from 50:1 to 1:50.

9. A kit of parts comprising:
(i) a vessel containing an inhibitor of carboxypeptidase U, or a pharmaceutically acceptable salt thereof;
(ii) a vessel containing a thrombin inhibitor, or a derivative thereof;
and instructions for the sequential, separate or simultaneous administration of the inhibitors (i) and (ii) to a patient in need thereof.

10. The kit of parts according to claim 9, wherein the inhibitor of carboxypeptidase U is a compound as defined in claim 2 or 3.

11. The kit of parts according to claims 9 or 10, wherein the thrombin inhibitor is a low molecular weight thrombin inhibitor.

12. The kit of parts according to claim 11, wherein the low molecular weight thrombin inhibitor is a peptide-based, amino acid-based, and/or peptide analogue-based, thrombin inhibitor with one to four peptide linkages.

13. The kit of parts according to claim 12, wherein the low molecular weight thrombin inhibitor is HOOC-CH_2-(R)Cgl-Aze-Pab-H or a prodrug thereof.

14. The kit of parts according to claim 13, wherein the prodrug is EtOOC-CH_2-(R)Cgl-Aze-Pab-OH.

15. The kit of parts according to any one of claims 9 to 14, wherein the molar ratio between the inhibitor of carboxypeptidase U and the thrombin inhibitor lies in the range of from about 1000:1 to about 1:1000, preferably from 50:1 to 1:50.

16. A kit of parts comprising:
(i) a pharmaceutical formulation containing an inhibitor of carboxypeptidase U, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier; and
(ii) a pharmaceutical formulation containing a thrombin inhibitor, or a derivative thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier;
which inhibitors (i) and (ii) are each provided in a form that is suitable for administration in conjunction with the other.

17. The kit of parts according to claim 16, wherein inhibitors (i) and (ii) are suitable for sequential, separate or simultaneous administration.

18. The kit of parts according to claim 16 or 17, wherein the inhibitor of carboxypeptidase U is a compound as defined in claim 2 or 3.

19. The kit of parts according to any one of claims 16 to 18, wherein the thrombin inhibitor is a low molecular weight thrombin inhibitor.

20. The kit of parts according to claim 19, wherein the low molecular weight thrombin inhibitor is a peptide-based, amino acid-based, and/or peptide analogue-based, thrombin inhibitor with one to four peptide linkages.

21. The kit of parts according to claim 20, wherein the low molecular weight thrombin inhibitor is HOOC-CH_2-(R)Cgl-Aze-Pab-H or a prodrug thereof.

22. The kit of parts according to claim 21, wherein the prodrug is EtOOC-CH_2-(R)Cgl-Aze-Pab-OH.

23. The kit of parts according to any one of claims 16 to 22, wherein the molar ratio between the inhibitor of carboxypeptidase U and the thrombin inhibitor lies in the range of from about 1000:1 to about 1:1000, preferably from 50:1 to 1:50.

24. A formulation according to any one of claims 1 to 8, or a kit of parts according to any one of claims 9 to 23, for use in medical therapy.

25. A method for treatment of a patient suffering from, or susceptible to, a condition in which inhibition of thrombin and/or inhibition of carboxypeptidase U are required or desired, which method comprises administering to the patient a therapeutically effective total amount of
(i) an inhibitor of carboxypeptidase U, or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier; in conjunction with
(ii) a thrombin inhibitor, or a derivative thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

26. The method according to claim 25, wherein the administration of inhibitors (i) and (ii) is sequential, separate or simultaneous.

27. The method according to any one of claims 25 to 26, wherein the inhibitor of carboxypeptidase U is a compound as defined in claim 2 or 3.

28. The method according to any one of claims 25 to 27, wherein the thrombin inhibitor is a low molecular weight thrombin inhibitor.

29. The method according to claim 28, wherein the low molecular weight thrombin inhibitor is a peptide-based, amino acid-based, and/or peptide analogue-based, thrombin inhibitor with one to four peptide linkages.

30. The method according to claim 30, wherein the low molecular weight thrombin inhibitor is HOOC-CH_2-(R)Cgl-Aze-Pab-H or a prodrug thereof.

31. The method according to claim 30, wherein the prodrug is EtOOC-CH_2-(R)Cgl-Aze-Pab-OH.

32. The method according to any one of claims 25 to 31, wherein the molar ratio between the inhibitor of carboxypeptidase U and the thrombin inhibitor lies in the range of from about 1000:1 to about 1:1000, preferably from 50:1 to 1:50.

33. A method for treatment of a patient suffering from, or susceptible to, a condition in which inhibition of thrombin and/or inhibition of carboxypeptidase U are required or desired, which method comprises administering to the patient a formulation as defined in any one of claims 1 to 8.

34. The use of a formulation according to any one of claims 1 to 8, in the manufacture of a medicament for the treatment of a condition in which inhibition of thrombin and/or inhibition of carboxypeptidase U are required or desired.

35. The use according to claim 34, wherein the inhibitor of carboxypeptidase U is a compound as defined in claim 2 or 3.

36. The use according to claim 34 or 35, wherein the thrombin inhibitor is a low molecular weight thrombin inhibitor.

37. The use according to claim 36, wherein the low molecular weight thrombin inhibitor is a peptide-based, amino acid-based, and/or peptide analogue-based, thrombin inhibitor with one to four peptide linkages.

38. The use according to claim 37, wherein the low molecular weight thrombin inhibitor is HOOC-CH_2-(R)Cgl-Aze-Pab-H or a prodrug thereof.

39. The use according to claim 38, wherein the prodrug is EtOOC-CH_2-(R)Cgl-Aze-Pab-OH.

40. The use according to any one of claims 34 to 39, wherein the molar ratio between the inhibitor of carboxypeptidase U and the thrombin inhibitor lies in the range of from about 1000:1 to about 1:1000, preferably from 50:1 to 1:50.

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